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281 MOLECULAR MECHANISM OF SKIN IRRITATION AFTER ACUTE EXPOSURE TO *m*-XYLENE IN RATS AND GUINEA PIGS.

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Organic solvents like xylene are recognized as a skin irritant after dermal exposure. The molecular responses to organic solvents that result in acute irritation are not understood. In the present study, we compared and quantified the molecular responses of rat and guinea pig skin to xylene irritation, since these species differ in their response to other chemicals. Animals were exposed to *m*-Xylene (250 µl) on their shaved back for 1hr using Hill Top Chambers. Zero, one, three and five hrs after the exposure treated and sham treated skin samples (1g) were collected and homogenized with Tris buffer. Supernatants were used to measure the early markers of skin irritation. Western blot analysis revealed that IL-1α protein levels increased 3 fold more in rats than in guinea pigs within one hr after xylene exposure. In contrast, iNOS protein induction was four-fold greater in guinea pigs than in rats. In rats the changes in iNOS levels were comparable to the changes in IL-1α levels but occurred two hours later. NO levels, determined by Griess reagent, were elevated four fold two hours after the beginning of the xylene exposure in rats. However, in guinea pigs, only a slight change of NO level was observed. In addition, immunohistochemical localization revealed that immunopositive cells for IL-1α and iNOS were detected more predominantly in the epidermis of guinea pig skin than in rat. An oxidant-sensitive fluorescence dye, DCF-DA was used as a probe to detect free radical generation in order to compare the intensity of oxidative stress formed due to xylene exposure in these species. These results suggest that the skin's molecular and biological response to xylene exposure occur earlier in guinea pigs than in rats. (Supported by CDC/NIOSH RO1 OH03654-03.)

282 HYDRATION *VERSUS* SKIN PERMEABILITY TO NICOTINATES IN MAN.

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Prolonged occlusion increases skin water content and often increases permeability and irritant dermatitis. We defined the quantitative relationship between nicotinates permeability and hydration as measured by water evaporation rate (WER) decay curves and WER-area under the curve (WER-AUC); also determined the level of skin hydration and permeability to nicotinates following a diapering simulation. 9 women were enrolled; each received three wet occlusive patches for 10 min, 30 min, and 3 h; and two wet diapers (3 and 8 h). Basal values of WER, blood flow volume (BFV), capacitance (Cap) and redness (a*) were measured on pre-marked sites. Immediately, following occlusive patch or diaper removal, each nicotinate (methyl and hexyl) was applied to its respective site. WER and Cap were recorded at designated sites at 0, 5, 10, 15 and 20 min; a* and BFV at 5, 10, 15, 20, 30, 40, and 60 min after nicotinate applications. WER-AUC and skin hyperhydration increased with occlusive patch and diaper exposure time, but no statistical difference between 3 and 8 h diaper. All patched sites had significantly ($p<0.05$) increased hydration in comparison to control site. Cap increased with occlusion time with patches, but not with diapers. The degree and time-course of redness from nicotinates did not vary with extent of skin hydration, but was significantly increased compared to non-hydrated skin. BFV-AUC did not show a significant increase between diapers at 3 and 8 h sites; BFV-AUC values varied on the patched sites but some were significantly ($p<0.05$) higher than control site. We found no evidence of increased permeation rates with increased hyperhydration once a relatively low threshold of hyperhydration was achieved and also suggested that the WER-AUC method was superior to capacitance for measuring the absolute extent of hyperhydration. We believe this is a suitable model in evaluating the quality of diaper product performance.

283 DAILY DERMAL CO-EXPOSURE OF RATS TO DEET AND PERMETHRIN PRODUCES SENSORIMOTOR DEFICIT, AND CHANGES IN BLOOD-BRAIN BARRIER (BBB) AND BLOOD-TESTIS BARRIER (BTB).

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In the present study we investigated the effects of daily dermal application of DEET and permethrin, alone or in combination, on sensorimotor performance and the permeability of the BBB and BTB in male Sprague-Dawley rats. Groups of five rats were treated with a dermal daily dose of 4, 40, or 400 mg/kg DEET in ethanol or 0.013, 0.13, or 1.3 mg/kg permethrin in ethanol for 60 days. A group of ten rats received a daily dermal dose of ethanol and served as controls. BBB permeability was assessed by injection of an i.v. dose of the quaternary ammonium compound [^{3}H]hexamethonium iodide. While permethrin produced no effect on BBB permeability, DEET alone caused a decrease in BBB permeability in brainstem. A combination of DEET and permethrin significantly decreased the BBB permeability in the cortex. BTB permeability was decreased by treatment DEET alone and in combination with permethrin. The same animals underwent a battery of functional behavior tests 30, 45, and 60 days after exposure to evaluate their sensorimotor abilities. All treatments caused a significant decline in sensorimotor performance in a dose-and time-dependent manner. These results show that daily dermal exposure to DEET, alone or in combination with permethrin decreased BBB permeability in certain brain regions, and impaired sensorimotor performance. Supported, in part by the U. S. Army Medical Research and Materiel Command under contract #DAMD 17-99-1-9020. The views, opinion and/or findings contained in this report are those of the authors and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

284 USED SEMI-SYNTHETIC METAL WORKING FLUID (UMWF): DERMAL AND SYSTEMIC EFFECTS IN B6C3F1 MICE.

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In our previous studies we demonstrated that dermal exposure to unused MWF caused a significant increase in skin histamine, mast cell numbers, malondialdehyde (MDA), and alcohol dehydrogenase (AD) and reduction in ascorbic acid (AA) levels. In use, MWF becomes contaminated with microorganisms (*e.g.*, gram negative bacteria) and their products (endotoxin) which may alter the toxicity of these fluids. To complement the previous studies, a sample of MWF used for 11 months and contained approximately 5000 endotoxin units (EU)/ml was tested. Unshaven mice of both sexes at 6 weeks of age were topically given 200ll of used MWF 2 days a week for 6 weeks. Total skin histamine (both sexes), testicular and liver AA (both sexes), and MDA (female liver) were reduced significantly ($P < 0.05$) compared to untreated control groups. Similar reductions of AA and MDA were observed when mice were topically exposed to endotoxin alone at 5000EU/ml. The AD levels in the male (testes and liver) were similar to those in controls; however, the AD levels in the treated female livers were increased when the mice were exposed to used MWF or to 5000 EU/ml of endotoxin alone. These results suggest that the toxic effects of used MWF were different than those observed with unused MWF and that differences were largely due to the endotoxin contamination of the MWF.

285 ACUTE DERMAL TOXICITY OF A NICOTINE MIXTURE.

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A study was conducted with Sprague-Dawley rats to estimate the acute dermal toxicity of a mixture containing 18% (w/w) nicotine and 82% of an ion-exchange resin. The primary purpose of the study was to define toxicity of this mixture used in manufacturing a smoking cessation product for purposes of workplace hazard labeling. Based on concentration present in the mixture and dermal toxicity of nicotine alone, in the absence of data for the mixture, current regulations would require labeling this mixture as VERY TOXIC. Moistened nicotine mixture was first applied under semi-occluded conditions to shaved backs and flanks of one male and one female rat at a total dose level of 2000 mg/kg following OECD Guidelines for dermal toxicity (No. 402 "Acute Dermal Toxicity"). The application area was covered for 24 hours, then rinsed with water to remove the nicotine mixture . Animals were observed for signs of toxicity 0.5, 1, 2 and 4 hours after treatment and once daily for fourteen days then subjected to gross necropsy. Based on the absence of findings in this preliminary evaluation, 4 additional rats of each sex were treated in the same way with the same dose of nicotine mixture. No detectable toxicity or treatment-related effects were observed in any treated rat based on clinical observation, direct effect on application site, body weight gain or gross necropsy. This nicotine mixture was non-toxic to rats *via* the dermal route and would require no workplace hazard labeling. Procedures for estimating toxicity of this mixture, based only on concentration and dermal toxicity of nicotine, would significantly overestimate the actual acute dermal toxicity of this mixture.